IN THE CLAIMS

Please cancel claims 6 through 8.

Please add new claims 9 to 18.

Please substituted enclosed amended claims 1 through 5 for claims 1 through 5 presently on file.

REMARKS

The claim changes indicated above are intended to affect amendment of the claims in this application to add the same claims (now renumbered) as provided with the response of 28 November 2001.

The applicant repeats below substantially the remarks provided in the responses of 28 November 2001 and 9 April 2002, now amended to reflect the revised claim numbering.

Claim Amendments Relating to Nitric Oxide Agonists

The applicant has amended claims 1 through 5 and added new claims 9 through 18. Claim 1 (as amended) and new claims 10, 11, 12, 13, 15 and 18 are now directed, *inter alia*, to methods or compositions involving nitric oxide agonists. Support for these claims can be found in the specification and particularly at page 8, line 12, and page 10, line 14.

Claim Objections

The applicant has amended claim 1, pursuant to the Examiner's objection, to make reference to a mammalian patient to whom the compound is administered.

Claims 6 to 8 as originally filed have been cancelled.

The applicant has amended claim 1 to be directed to a method of increasing insulin sensitivity by administering an effective amount of a nitric oxide donor or nitric oxide agonist compound. This amendment was made for reasons unrelated to the art cited against this claim by the Examiner. Argument with respect to the art cited by the Examiner follows.

35 USC § 102

Claims 1-4

Petrie *et al.* discloses the separate administration of either a nitric oxide synthesis inhibiting compound (L-NMMA), a stimulator of nitric oxide synthase (acetylcholine), or a nitric oxide donor (sodium nitroprusside) to the brachial artery, for delivery directly to vasculature within skeletal muscle.

Petrie reports a correlation between reduced insulin sensitivity and the response to L-NMMA, an inhibitor of nitric oxide synthase, but no correlation between insulin sensitivity and responses to the stimulator of nitric oxide synthase (acetylcholine) or the nitric oxide donor (sodium nitroprusside). (See Results section third and fourth sentences before the end, as well as the final line in the "Methods and Results" portion of the Abstract.)

As no correlation between insulin sensitivity and the response to a stimulator of nitric oxide synthase, nitric oxide donor or nitric oxide agonist was shown, Petrie does not teach a method of increasing insulin sensitivity. In fact, Petrie's reported failure to obtain an increase in insulin sensitivity underscores the surprising and novel nature of the present invention.

Thus, the applicant submits that claim 1, and dependent claims 2 through 9, are not anticipated by Petrie *et al.*

Claim 5

The applicant has amended claim 5 to more clearly indicate that the pharmaceutical composition of interest comprises, *inter alia*, an amount of a nitric oxide donor compound effective to cause an increase in nitric oxide in the liver.

The applicant has further amended claim 5 to indicate that the compound is a nitric oxide donor compound. This amendment was made for reasons unrelated to the art cited against these claims by the Examiner. Argument with respect to the art cited by the Examiner follows.

The references cited by the Examiner with respect to original claims 5 through 7 as filed disclose various compositions including stimulants of nitric oxide synthesis, or nitric oxide donors, with pharmaceutically acceptable carriers. However, these references do not teach amounts of the nitric oxide producing compounds effective to cause an increase in nitric oxide in the liver.

Thus, the applicant submits that claim 5 as amended, and dependent claims 11 to 14 are novel and non-obvious in light of the cited art.

35 USC § 103

The applicant submits that Petrie *et al.* is inapplicable to the claims as amended for the reasons previously discussed. In particular, Petrie neither teaches nor suggests a role for nitric oxide donors or nitric oxide agonists in increasing insulin sensitivity. Thus, the applicant submits that the pending claims are non-obvious in light of the cited art.

New Claims 15 to 18

For the reasons which follow, the applicant submits that newly added claims 15 through 18 are patentable over the cited references.

Claim 15

New claim 15 is directed to a pharmaceutical composition comprising an effective amount of a nitric oxide agonist, and a pharmaceutically acceptable carrier.

The cited references neither disclose nor suggest a composition containing a nitric oxide agonist.

The reference of Petrie, cited by the Examiner, reports a correlation between reduced insulin sensitivity and the response to an inhibitor of nitric oxide synthase. However, Petrie neither reports nor suggests a correlation between insulin sensitivity and responses to acetylcholine or sodium nitroprusside, which compounds would be expected to increase nitric oxide levels. Thus, Petrie neither teaches nor suggests that the use of a nitric oxide agonist would increase insulin sensitivity.

As the cited art neither teaches pharmaceutical compositions including nitric oxide agonists, nor suggests their usefulness to increase insulin sensitivity, the applicant submits that new claim 15 is novel and non-obvious in light of the cited art.

Claims 16 to 18

Claim 16, and claims 17 and 18 dependent upon it, are directed to a kit comprising at least one of a nitric oxide donor or a nitric oxide agonist together with instructions for the administration of the nitric oxide donor or nitric oxide agonist to ameliorate the symptoms of insulin resistance.

As described with respect to new claim 15, above, the cited art neither teaches nor suggests compositions containing a nitric oxide agonist or a role for nitric oxide agonists in reducing the symptoms of insulin resistance.

Moreover, as discussed with respect to claims 1 and 15, the cited references neither teach nor suggest use of either nitric oxide donors or nitric oxide agonists in ameliorating the symptoms of insulin resistance, nor do they provide a method or instructions for administering such compounds to overcome the symptoms of insulin resistance.

As the administration of a nitric oxide donor or nitric oxide agonist to ameliorate the symptoms of insulin resistance is neither taught nor suggested in the cited art, a kit comprising such instructions together with a nitric oxide donor or nitric oxide agonist is therefore novel and non-obvious in light of the cited art.

The applicant has received a form entitled "Attachment for PTO-948" relating to drawing changes. However, the applicant is not aware of any requisition with respect to the drawings pending in this application. If such a requisition is outstanding, the applicant respectfully requests that the Office notify the applicant as soon as possible.

The applicant has added a further independent claim by amendment. Kindly charge all applicable fees at the small entity rate to our deposit account 13-2400. Notification of charges made would be appreciated.

Favourable reconsideration and allowance of this application are respectfully requested.

Should the Examiner believe however that additional amendments to the claims may be required to secure allowance of this application, she is invited to telephone the undersigned at the below-noted number to facilitate further prosecution of this application.

This response is being forwarded via facsimile transmission to the Patent Examination Section, Fax No. (703) 308-4242, and we trust this will be in order.

Respectfully Submitted,

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By: _____

Mitchell B. Charness

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CLAIMS:

B1

1. A method of increasing insulin sensitivity in a mammalian patient by: administering to the patient an effective amount of a nitric oxide donor or nitric oxide agonist compound.

B2

2. The method according to claim 9, wherein said administering step further includes orally administering the compound.

3. The method according to claim 9 wherein said administering step further includes injecting the compound.

4. The method according to claim 9 wherein said administering step further includes delivering the compound through a pump system directly into the portal vein.

B3

5. A pharmaceutical composition useful to cause an increase in nitric oxide in the liver of a patient in need thereof, said composition comprising an amount of a nitric oxide donor compound, said amount being effective to cause an increase in nitric oxide in the liver, and a pharmaceutically acceptable carrier.

9. The method according to claim 1, wherein the compound is a nitric oxide donor compound.

10. The method according to claim 1, wherein the compound is a nitric oxide agonist compound.

9-17 has already been added

11. The method according to claim 10, wherein said administering step further includes orally administering the compound.

12. The method according to claim 10, wherein said administering step further includes injecting the compound.

13. The method according to claim 10 wherein said administering step further includes delivering the compound through a pump system directly into the portal vein.

14. The pharmaceutical composition of claim 10, wherein said donor is adapted to preferentially release nitric oxide in the liver.

15. A pharmaceutical composition useful in increasing insulin sensitivity in a mammalian patient, said composition comprising an effective amount of a nitric oxide agonist, and a pharmaceutically acceptable carrier.

16. A kit comprising:
at least one of a nitric oxide donor or a nitric oxide agonist; and,
instructions for the administration of said nitric oxide donor or nitric oxide agonist to ameliorate the symptoms of insulin resistance.

17. The kit of claim 16, including a nitric oxide donor.

18. The kit of claim 16, including a nitric oxide agonist.